REMARKS/ARGUMENTS

Claims 4 and 12 are pending in this application after entry of this Amendment. Claim 12 has been amended to clarify the subject matter Applicants consider to be the invention. Claims 1 and 3 are canceled herewith, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. No new matter has been added.

A. Rejection of Claims 1 and 3-4 under 35 U.S.C. § 112, first paragraph.

The Office action states that Claims 1 and 3-4 are rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. The Office action further states that the specification contains no proper antecedent basis for recitation of the limitation "antimetabolite," and therefore the limitation constitutes new matter.

Applicants respectfully traverse this rejection and direct the Examiner's attention to paragraph [0010] on page 4, and in particular line 12, of the specification filed on July 30, 2003 (paragraph [0009] of the specification as published in U.S. 2004/0097470). That paragraph reads (emphasis added):

> [0010] The present invention provides a novel use of linear alkylphosphocholines of the general Formulas I and II in an inventive combination with other medicinal drugs for the treatment of benign and malignant oncoses in humans and mammals. According to one aspect of the invention, the compounds of the general Formulas I and II can be used in an inventive combination with anti-tumor substances. Anti-tumor substances may be alkylating agents, **anti-metabolites**, plant alkaloids, platinum compounds, tumor antibiotics and agonists or antagonists of natural hormones. The anti-tumor substances may be selected from, but are not restricted to cis-platinum, carboplatinum, oxaliplatinum, bleomycin, doxorubicin, methotrexate, paclitaxel, docetaxel, vincristine, vinblastine, etoposide, teniposide, ifosfamide, cyclophosphamide, 5-fluorouracil, fludarabin, gemcitabin and cytarabin.

Applicants further contend that a person of ordinary skill in the art would have understood the meaning of the term "anti-metabolites" at the time that the present application

was filed. In support of this contention, Applicants direct the Examiner's attention to Table X-1 on page 1227 of Calabresi (already of record).

B. Rejection of Claims 1, 3-4 and 12 under 35 U.S.C. §103(a) as unpatentable over Nickel *et al.* (U.S. 6,696,428) ("Nickel") and Hilgard *et al.*, Cancer Chemother. Pharmacol., (1993) 32: 90-95 ("Hilgard") in view of Stekar *et al.* European J. of Cancer, (1995) Vol. 31(3) pp 372-374 ("Stekar") and Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition ("Calabresi").

The Office action states that the affidavit of Dr. Eckhard Guenther is insufficient to overcome this rejection because the evidence is not commensurate in scope to the claimed subject matter in that no trend has been demonstrated showing the unexpected results for compounds of formula II other than perifosine. Applicants have canceled Claims 1 and 3, and have amended Claim 12. These amendments limit the alkylphosphocholine to perifosine. Applicants believe that the cancellation of Claims 1 and 3, and the amendment of Claim 12 are sufficient to make Dr. Guenther's affidavit commensurate in scope with pending Claims 4 and 12. Moreover, applicants believe that the evidence of unexpected results set forth in Dr. Guenther's affidavit establishes that pending Claims 4 and 12 are non-obvious.

According to the Office action, the combined teachings of Nickel, Hilgard and Stekar would have motivated one of ordinary skill in the art to use perifosine to treat mammary carcinoma. Further, the Office action states that Table X-1 of Calabresi discloses antitumor agents such as 5-fluorouracil for treating cancer, and that one of ordinary skill in the art would expect the combined properties of the anti-tumor compounds to treat cancer, and that combination therapy may be synergistic through biochemical interactions.

Applicants respectfully traverse this rejection because a person of ordinary skill in the art would not have reasonably expected the claimed combination of perifosine and the cited antimetabolites to be more effective or synergistic for the treatment of mammary carcinoma than either drug alone. Whether a particular combination of anticancer agents will be synergistic against a particular cancer is not predictable. Calabresi points out that drug combinations ***may be*** synergistic. However, as detailed in the 1984 Chau and Talalay reference (already of record), a

drug combination may also be additive or antagonistic. *See, e.g.*, page 35. An additive drug combination occurs when the overall effect is the sum of the effect that each drug alone would impart. An antagonistic drug combination results when the combination of drugs is less effective than either drug alone. A drug combination might exhibit any of these possibilities (synergy, additivity, or antagonism) in a particular type of cancer.

Moreover, the synergy observed using the combination of perifosine and antimetabolites could not have been predicted based on the prior art. Hilgard 1996 (*Heterocyclic Alkylphospholipids With An Improved Therapeutic Range*, already of record) teaches that the combination of perifosine and cyclophosphamide demonstrates "some evidence of additive or synergistic effects[]" against mammary carcinoma. *See* page 163. However, a person of ordinary skill in the art would have recognized that cyclophosphamide has a different mechanism of action than an antimetabolite. Cyclophosphamide, an alkylating agent, alkylates DNA or RNA thereby causing strand cross-linking and strand breaking, leading to inhibition of DNA or protein synthesis. Antimetabolites, such as 5-fluorouracil, fludarabine, gemcitabine and cytarabine, on the other hand, do not alkylate DNA or RNA. These antimetabolites act primarily by inhibiting enzymes involved in DNA synthesis. 5-Fluorouracil, for example, inactivates thymidylate synthase – an enzyme required for synthesis of thymidine (*i.e.*, a component of DNA). Because these mechanisms of action are different, a person of ordinary skill in the art would have recognized that the sensitivity and/or resistance of a particular cancer to cyclophosphamide would be different than the sensitivity and/or resistance to an antimetabolite. Therefore a person of ordinary skill in the art would not expect the combination of perifosine with an antimetabolite to be synergistic just because the combination of perifosine with cyclophosphamide is synergistic.

C. Provisional Double Patenting Rejections

Applicants note that Claims 1, 3-4 and 12 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over Claims 1-19 of U.S. Patent Application Number 12/751,608 and Claims 1-14 of U.S. Patent Application Number 12/751,454.

Applicants believe that after the current amendments, these provisional double patenting rejections will be the only remaining rejections of record. Accordingly, applicants request that the pending claims be allowed, and that double patenting rejections be made in pending applications U.S. 12/751,608 and U.S. 12/751,454. (*See* MPEP § 804 I.B.1, pages 800-17 to 800-18.)

CONCLUSION

Based on the foregoing amendments and remarks, favorable consideration and allowance of all of the claims now present in the application are respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawings be further amended or corrected in formal respects in order to place the case in condition for final allowance, then it is respectfully requested that such amendment or correction be carried out by Examiner's Amendment and the case be passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to telephone the undersigned.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

Dated: March 3, 2011

Respectfully submitted,

Electronic signature: /Timothy J. Doyle/
Timothy J. Doyle
Registration No.: 58,127
GOODWIN PROCTER LLP
The New York Times Building
620 Eighth Avenue
New York, New York 10018
(212) 459-7483
Agent for Applicant